# Single Trial FMRI: The Optimal Inter-Stimulus Interval

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Introduction: Recent studies have shown that functional MRI can detect signal changes resulting from brief (under 2 s) increases in neural activity (1,2). In this work, we investigate the trade-off in the choice of inter-stimulus interval (ISI): a longer ISI makes the BOLD responses from distinct stimuli well separated and allows a clear return to baseline, but shorter ISI allows more responses to be measured, improving detectability. We assume that a train of identical stimuli is applied, with the ISI denoted by $T$.

Signal Model: We assume that the MR signal response is given by a shift-invariant filter applied to the underlying "neural activity" in each voxel. The response to a single stimulus is proportional to a given function $r(t)$. We assume that the noise is stationary and white. The signal in each voxel is modeled by

$$\begin{aligned} x(t) &= \alpha \cdot \sum_{m=0}^{M-1} r(t-mT) + \beta + \zeta(t) \\ x_n &= \alpha \sum_m r_{n-Lm} + \beta + \zeta_n \qquad (n = 1, 2, \ldots, N) \\ \mathrm{x} &= \underbrace{\left[ \mathrm{r}^{(L)} \ \mathrm{e}_N \right]}_{\equiv \mathrm{P}} \begin{bmatrix} \alpha \\ \beta \end{bmatrix} + \zeta \,. \end{aligned}$$

Here, $\alpha$ is the response magnitude, $\beta$ is the baseline, and $\langle\zeta\rangle = 0$, $\langle\zeta\zeta^*\rangle = \sigma^2 \mathrm{I}$. The $N$-vector $\mathrm{r}^{(L)}$ is defined by $r_n^{(L)} = \sum_m r_{n-Lm}$; the $N$-vector $\mathrm{e}_N$ is all 1s. The goal is to estimate $\alpha$, but $\beta$ is also unknown. The total length of the experiment is $ML\Delta t = N\Delta t$; $\Delta t$ is the sampling interval, $T = L\Delta t$, and $M$ is the number of stimuli.

Estimating $\alpha$: The minimum variance linear unbiased estimator of $\alpha$ and $\beta$ is

$$\begin{bmatrix} \hat\alpha \\ \hat\beta \end{bmatrix} = [\mathrm{P}^*\mathrm{P}]^{-1}\mathrm{P}^*\mathrm{x} \qquad \mathrm{Cov}\begin{bmatrix} \hat\alpha \\ \hat\beta \end{bmatrix} = \sigma^2 [\mathrm{P}^*\mathrm{P}]^{-1}$$

$$\begin{aligned} \mathrm{P}^*\mathrm{P} &= \begin{bmatrix} \sum_n (r_n^{(L)})^2 & \sum_n r_n^{(L)} \\ \sum_n r_n^{(L)} & N \end{bmatrix} \\ \mathrm{Var}(\hat\alpha) &= \frac{N\sigma^2}{N\sum_n (r_n^{(L)})^2 - (\sum_n r_n^{(L)})^2} \end{aligned}$$

Nonoverlapping Responses: If the stimuli are spaced far enough apart so that the responses do not significantly overlap, then $r_n^{(L)} = r_{n-L\lfloor n/L \rfloor}$, so

$$\sum_n (r_n^{(L)})^q = M \sum_{n=0}^{L-1} r_n^q \approx M\Delta t^{-1}\mu_q \,,$$

where $\mu_q \equiv \int_{-\infty}^{\infty} r(t)^q \, dt$. This integral approximation is valid if $\Delta t$ is small compared to the rise and fall times of the response function.

We want to minimize $\mathrm{Var}(\hat\alpha)$ for a fixed amount of scan time $N\Delta t$ by choosing the ISI $L\Delta t$ properly. We can write $M = N/L$, and then

$$\frac{1}{\mathrm{Var}(\hat\alpha)} \approx \frac{N}{\sigma^2} \cdot \frac{1}{L\Delta t}\left(\mu_2 - \frac{1}{L\Delta t}\mu_1^2\right)$$

Minimizing $\mathrm{Var}(\hat\alpha)$ w.r.t. the ISI $T = L\Delta t$, we find

$$T_{\mathrm{opt}} = 2\frac{\mu_1^2}{\mu_2} = 2\frac{\left(\int r(t)\,dt\right)^2}{\int r(t)^2\,dt} \,.$$

This is equivalent to maximizing the expected value of $\int_0^{N\Delta t} |x(t) - \bar{x}|^2 \, dt$, which shows that the optimum ISI is based on balancing the time budget between the stimulus response and the baseline state.

Examples: The simplest response function is a 'boxcar':

$$r_\square(t;\tau) = \begin{cases} 1 & 0 < t < \tau \\ 0 & \text{otherwise.} \end{cases}$$

In this case $\mu_1 = \mu_2 = \tau$, and so $T_{\mathrm{opt}}^\square = 2\tau$; that is, equal times should be spent in the stimulus response and in the baseline. A little more realistic is the triangle response:

$$r_\triangle(t;\tau) = \begin{cases} 1 - \tau^{-1}|t-\tau| & 0 < t < 2\tau \\ 0 & \text{otherwise,} \end{cases}$$

yielding $\mu_1 = \tau$ and $\mu_2 = 2\tau/3$, so $T_{\mathrm{opt}}^\triangle = 3\tau$. In this case, the optimal balance is to spend $\frac{1}{3}$ the time in the baseline and $\frac{2}{3}$ in the stimulus response. For FMRI, a reasonable estimate of the rise/fall time is $\tau = 5$ s, giving $T_{\mathrm{opt}}^\triangle = 15$ s.

For the gamma variate response function (3), we have

$$\begin{aligned} r_\Gamma(t;b,c) &= \begin{cases} t^b e^{-t/\tau} & t > 0 \\ 0 & \text{otherwise} \end{cases} \\ T_{\mathrm{opt}}^\Gamma &= \frac{2b\,4^b\,\Gamma(b)^2}{\Gamma(2b)} \cdot \tau \,. \end{aligned}$$

Realistic values for BOLD FMRI are $b = 8.6$, $\tau = 0.55$ s, giving $T_{\mathrm{opt}}^\Gamma = 11.6$ s. If the stimulus duration is extended to last 2 s, then with $r(t) = r_\square(t;2) \star r_\Gamma(t;8.6,0.55)$, we find that $T_{\mathrm{opt}}^{\square\star\Gamma} = 12.3$ s.

Conclusion: Based on these and other examples, our theoretical conclusion is that for short duration stimuli (under 3 or 4 s), an inter-stimulus interval of about $T = 15$ s is optimal. Larger values of $T$ waste acquisition time; shorter values of $T$ do not allow accurate estimation of the response amplitude. For stimuli of duration longer than 4 s, adding an extra 2 s to $T$ for every extra 1 s of stimulation is needed. The theoretical results presented here have been confirmed by FMRI experiments in humans; that work is presented elsewhere at this conference. Work is now underway to extend this theory to the cases where the stimuli are not identical and where the responses may overlap.

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